DERIVATIVES OF 3,2′-NICOTYRINE AND THEIR STRUCTURES

BY

HAROLD JOHN WATSON

A.B., Princeton University, 1944
A.M., University of Illinois, 1948

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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Introduction

Nicotine, being among the most abundant and least expensive alkaloids, offers promise as raw material for the synthesis of compounds having pharmaceutical or insecticidal uses.

Its dehydrogenation product, 1-methyl-2-(3-pyridyl)-pyrrole, called 3,2′-nicotyrine or simply nicotyrine, is a useful intermediate in the preparation of synthetic alkaloids, since the pyrrole nucleus will undergo various substitution reactions characteristic of aromatic rings. Acetylation(1), benzoylation (2),iodination (3), and coupling with diazonium compounds (4) have been carried out upon nicotyrine. Two of these reactions have been carried one step further; iodonicotyrine has been converted to cyanonicotyrine (3), and a nicotyrine azo dye has been reduced to aminonicotyrine (4). In none of these cases has the proof of the positions of the substituents been given.

The purpose of the work described herein was to prepare various derivatives of nicotyrine, to relate them to each other by interconversion, and to show the positions on the pyrrole nucleus held by the several substituents.

Discussion

Iodination of nicotyrine in alkaline solution forms 5′-iodo-3,2′-nicotyrine, as is shown below. This compound was converted to the corresponding cyano compound, m.p. 72°, which was hydrolyzed to the acid, m.p. 204°. The acid was converted to the ester, m.p. 36°, and the amide, m.p. 168°. The same acid was formed by hypochlorite oxidation of the acetylnicotyrine which melts at 54°, made by the method of Haines and Eisner (5). Reduction of this acetylnicotyrine gave a

liquid ethylnicotyrine, the picrate of which melts at 169°. These compounds, therefore, all have the same configuration.

A different acetylnicotyrine, which melts at 109°, has been formed as well. Oxidation and reduction gave, respectively, an acid, m.p. 167°, and an ethylnicotyrine, the picrate of which melts at 150°. Addition of bromine to nicotyrine followed by neutralization gave a bromonicotyrine, the picrate of which melts at 181°. This was converted to the corresponding cyano compound, m.p. 100.5°, which on hydrolysis gave the same acid, m.p. 167°. Benzoylation of nicotyrine gave the same compound as was formed by the addition of diphenylcadmium to the acid chloride of the acid of m.p. 167°. These compounds thus have the same configuration, in which, as is shown below, the substituents are on the 4′-position. Coupling of the two above nicotyrinecarboxylic acids gave, respectively, azo compounds in which the carboxyl group was replaced and retained. This indicates that the carboxyl group of the acid, m.p. 204°, is in the 5′-position, since it has been observed (6) in the pyrrole series that an α-carboxyl group can be replaced by an azo linkage, and that α-substitution is preferred to β-substitution. Decarboxylation of the azo dye formed from the acid of m.p. 167° gave the same azo dye as was formed directly from the acid of m.p. 204°. Coupling of nicotyrine gave the same azo dye as coupling of the acid of m.p. 204°. This indicates that the coupling occurs at the 5′-position in all cases.

Of the two remaining positions on the pyrrole nucleus, the 3′-position seems unlikely for steric reasons as the position of the substituents of the compounds related to the acid of m.p. 167° (benzoylnicotyrine is a member of this group). This leaves the 4′-position as the logical choice for the substituents of the compounds in this group. Haines and Eisner (5) have prepared the two isomeric acetylnicotyrines and compared their ultraviolet absorption spectra with those of 2- and 3-acetyl-5-phenyl-1-methylpyrrole. On the basic of the similarities in absorption spectra, they concluded that the low-melting acetylnicotyrine is the 5′-isomer and the high-melting acetylnicotyrine is the 4′-isomer.

In conclusion, it can be stated that the following facts are reasons for assigning the 4′-position to the substituents of the compounds related to the acid of m.p. 167°, and the 5′-position to the substituents of the compounds related to the acid of m.p. 204°:

a. Replacement of the carboxyl group of the acid of m.p. 204° by entering azo groups.

b. Greater ease of α-substitution by diazonium salts.

c. Ultraviolet absorption spectrum studies by Haines and Eisner.

d. Steric hindrance which would attend benzoylation of nicotyrine in the 3′-position.

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VITA

The author was born in San Francisco, California, on July 7, 1923. He attended public and private schools of Sausalito, California, and St. Louis, Missouri, and was graduated from St. Louis Country Day School in June, 1940. He entered Princeton University in September, 1940, and received the degree of Bachelor of Arts in June, 1944. From May, 1944, until September, 1946, he served in the United States Naval Reserve as Engineer Officer. He entered the University of Illinois in September, 1946, and received the degree of Master of Arts in chemistry in June, 1948. He was an Assistant in Chemistry at the University of Illinois from September, 1946, to January, 1947, and a University of Illinois Fellow in Chemistry from February, 1948, to January, 1949, and from September, 1949, to January, 1950.